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Health and Environmental Effects Profile for Chloroacetaldehyde

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HEALTH AND ENIVIRONMENTAL EFFECTS PROFILE FOR CHLOROACETALDEHYDE

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16. ABSTRACT

The Health and Environmental Effects Profile for Chloroacetaldehyde was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Chloroacetaldehyde has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for chloroacetaldehyde is 0.007 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

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This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constit- uents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Chloroacetaldehyde (107-20-0) is a colorless liquid with an acrid, penetrating odor. Texas Eastman Co. manufactured 1-10 million pounds of chloroacetaldehyde in 1977 and two other companies imported this compound (reported import volume was <1000 pounds) (U.S. EPA, 1985a). Chloroacetaldehyde is used as a chemical intermediate, to manufacture 2-aminotriazole, as a fungicide to facilitate removal of bark from tree trunks, and it also has applications in dentistry (U.S. EPA, 1985b; Windholz, 1983; Lawrence and Autian, 1972).

Osterman-Golkar (1984) indicated that hydrolysis of chloroacetaldehyde is not an environmentally significant reaction ($t_{1/2}$>16 years). Volatilization has been predicted to be significant from shallow river waters, but it can be expected to take place slowly from other surface waters. Water solubility and K_{ow} data suggest that adsorption to suspended solids and sediments and bioaccumulation in aquatic organisms are not likely. The estimated hydroxyl reaction half-life of 8 hours indicates that this reaction is probably a significant mechanism for removal of chloroacetaldehyde from the atmosphere. Structural analysis of chloroacetaldehyde indicates that this compound is likely to be leached through soils.

No monitoring data are available to indicate ambient air or water levels, drinking water or food contamination or dermal exposure. Potential sources of chloroacetaldehyde entering the environment are from production and processing sites and use as a fungicide. Ando and Sayoto (1984) suggested that VCM can migrate from water pipes made of polyvinyl chloride, and that reaction of VCM and chlorine is a possible source of chloroacetaldehyde in drinking water. Another possible source of chloroacetaldehyde in

the atmosphere is formation from reaction of 1,3-dichloropropene with ozone and OH radicals (Tuazon et al., 1984). 1,3-Dichloropropene is a highly volatile component of widely used insecticidal fumigants (Tuazon et al., 1984).

Little information is available about the toxicity of chloroacetaldehyde to aquatic organisms. The 96-hour LC_{50} for the copepod, Nitocra spinipes, was 1.5 mg/ℓ (Bengtsson and Tarkpea, 1983), but sea lampreys were unaffected by exposure to 5 mg/ℓ for 24 hours (Applegate et al., 1957).

Pertinent data regarding the absorption, distribution or excretion of chloroacetaldehyde could not be located in the available literature as cited in the Appendix. Chloroacetaldehyde is a major metabolite of a number of chlorinated compounds (U.S. EPA, 1980a). After oral administration to rats, chloroacetaldehyde is first conjugated with glutathione and subsequently metabolized along two pathways (Green and Hathway, 1977). Urinary metabolites include N-acetyl(2-hydroxyethyl) cysteine S-(carboxymethyl) cysteine and thiodiglycollic acid.

Chloroacetaldehyde has been found not to increase tumorigenesis when given repeatedly to mice by topical, subchronic or intragastric routes of administration (van Duuren et al., 1979). Weekly intragastric administration, using one dose level (0.25 mg/mouse), did not affect forestomach tumor incidence, relative to negative control rats. Administration of the positive control, β-propiolactone, on the same schedule significantly ($p<0.0005$) enhanced forestomach tumor incidence. By all routes of administration, chloroacetaldehyde did not affect longevity. Mortality rates were adversely affected by repeated β-propiolactone administration. A single initiation dose of chloroacetaldehyde, followed by thrice weekly promotion, did not increase the incidence of skin papillomas, relative to control rates (van

Duuren et al., 1979; Zajdela et al., 1980). In none of these studies were attempts to define a dose-effect relationship made. There were no data regarding human occupational or epidemiological exposure to chloroacetaldehyde.

Chloroacetaldehyde has been found to be mutagenic in Salmonella typhimurium (McCann et al., 1975), Bacillus subtilis (Phillips et al., 1980), Escherichia coli (Rosenkranz, 1977), and Streptomyces coelicolor (Bignami et al., 1980) prokaryotes, and also in Schizosaccharomyces pombe (Loprieno et al., 1977), Saccharomyces cerevisiae (Loprieno et al., 1977), and Aspergillus nidulans (Bignami et al., 1980) eukaryotes. It was moderately genotoxic to cultured Chinese hamster ovary cells (Huberman et al., 1975). In many of these studies the genotoxic effect was weak and specific for base-pair mutations. Additionally, the severe acute toxicity of chloroacetaldehyde may mask significant mutagenic expression.

No studies were found in the available literature regarding the reproductive effects of chloroacetaldehyde exposure.

Van Duuren et al. (1979) administered chloroacetaldehyde solution at a dose level of 0.25 mg/mouse once a week for life. There were no effects of this dose on longevity. Inhalation exposure to 1.6 ppm (5.1 mg/m^3) chloroacetaldehyde, 7 hours/day, 5 days/week for 6 months had no observable adverse effects on rats, guinea pigs, rabbits or mice (Dow, 1962).

Lawrence et al. (1972) administered chloroacetaldehyde by intraperitoneal injection to Sprague-Dawley rats, 3 times/week for 12 weeks. Upon necropsy predominant among rats given the high doses (0.0016 and 0.0032 mℓ/kg) were hematological changes and bronchopneumonia. In rats treated with 0.00032 or 0.0008 mℓ/kg, there were no remarkable treatment-related effects.

Chloroacetaldehyde has been found to be acutely lethal at low levels; the oral LD_{50} in rats and mice ranged from 82.3-103.1 mg/kg. Increased pentobarbital-induced sleep time in mice exposed by inhalation to 0.043 mg/m^3 for 31 seconds was also noted (Lawrence et al., 1972).

An ADI of 0.007 mg/kg/day or 0.49 mg/day for a 70 kg man was derived for a subchronic inhalation NOEL in several species (Dow, 1962), using an uncertainty factor of 1000. Data were not sufficient for deriving an RQ or an F factor. Structurally related compounds, such as formaldehyde and acetaldehyde, are known to be carcinogenic. Unlike the related compounds there is no inhalation data available to show carcinogenic activity of chloroacetaldehyde. Chloroacetaldehyde is mutagenic and a presumed intermediate in metabolic pathway of EDC (ethylenedichloride). Because of lack of enough evidence for its carcinogenicity, the overall weight of evidence indicates that chloroacetaldehyde could be classified as a possible carcinogen (Group C) or not classifed as a human carcinogen (Group D) (U.S. EPA, 1984). Accordingly, Group D compounds cannot be ranked on the CERCLA hazard ranking scheme.

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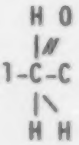
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BSP	Bromsulphalein
CHO	Chinese hamster ovary
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient standardized with respect to soil organic content
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LT_{50}	Lethal exposure time needed to kill 50% of recipients
MED	Minimum effective dose
NOEL	No-observed-effect level
PMA	Phobol myristate acetate
ppm	Parts per million
RQ	Reportable quantity
VCM	Vinyl chloride monomer

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Chloroacetaldehyde is also known as 2-chloro-1-ethanol and 2-chloro-acetaldehyde. The structure, CAS number, empirical formula and molecular weight are as follows:



Molecular weight: 78.50

Empirical formula: C_2H_3ClO

CAS Registry number: 107-20-0

1.2. PHYSICAL AND CHEMICAL PROPERTIES

At room temperature, chloroacetaldehyde is a clear, colorless liquid with an acrid, penetrating odor (Hawley, 1981; Windholz, 1983). It is soluble in water at concentrations <50%, but at concentrations >50% it forms an insoluble hemihydrate (U.S. EPA, 1985b). Selected physical and chemical properties are as follows:

Melting point (40% aqueous dil.):	-16.3°C	Hawley, 1981
Boiling point (40% aqueous dil.):	85°C	Hawley, 1981
Vapor pressure (calculated, 25°C):	62.3 mm Hg	Jaber et al., 1984
Log K_{ow}:	0.40	Jaber et al., 1984
Water solubility: at 25°C	1.4×10^5 mg/ℓ	Jaber et al., 1984
Flashpoint:	87.7°C	Hawley, 1981
Density (40% aqueous dil.):	1.19^{25}_{25}	Hawley, 1981
Refractive Index (40% aqueous dil., 25°C):	1.397	Hawley, 1981

1.3. PRODUCTION DATA

Chloroacetaldehyde has been manufactured by Texas Eastman Co. in Longview, TX (U.S. EPA, 1985a), which reported a production figure of 1-10 million pounds for 1977. International Flavors and Fragrances, Inc., imported <1000 pounds of chloroacetaldehyde, and Henley and Co., Inc., was listed as an importer but did not disclose their import volume.

Chloroacetaldehyde is prepared industrially by the controlled chlorination of acetaldehyde.

1.4. USE DATA

Chloroacetaldehyde is used to manufacture 2-aminothiazole, as a chemical intermediate, as a fungicide in the removal of bark from tree trunks, and it also has applications in dentistry (Lawrence and Autian, 1972; U.S. EPA, 1985b; Windholz, 1983).

1.5. SUMMARY

Chloroacetaldehyde is a colorless liquid with an acrid, penetrating odor. Texas Eastman Co. manufactured 1-10 million pounds of chloroacetaldehyde in 1977 and two other companies imported this compound (reported import volume for one was <1000 pounds) (U.S. EPA, 1985a). Chloroacetaldehyde is used as a chemical intermediate, to manufacture 2-aminotriazole, as a fungicide to facilitate removal of bark from tree trunks, and it also has applications in dentistry (U.S. EPA, 1985b; Windholz, 1983; Lawrence and Autian, 1972).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.2.1. Hydrolysis. Osterman-Golkar (1984) experimentally determined that chloroacetaldehyde has a hydrolysis half-life of <16 years.

2.2.2. Oxidation. Pertinent data regarding the oxidation of chloroacetaldehyde in water could not be located in the available literature as cited in the Appendix.

2.2.3. Photolysis. Data regarding the photolysis of chloroacetaldehyde in water could not be located in the available literature as cited in the Appendix.

2.2.4. Microbial Degradation. Data on the microbial degradation of chloroacetaldenyde in water could not be located in the available literature as cited in the Appendix.

2.2.5. Volatilization. No experimental volatilization data pertaining to chloroacetaldehyde were available; however, Henry's Law Constant was estimated to be 2.1×10^{-5} and 1.3×10^{-6} m^3-atm/mol, respectively, using the bond and group contribution methods of Hine and Mookerjee (1975). These values indicate volatilization from shallow rivers should be significant, although evaporation would be slow from other surface waters (Lyman et al., 1982).

2.2.6. Adsorption. No experimental data regarding the adsorption of chloroacetaldehyde to suspended solids and sediments in water were located, although the relatively high water solubility and low K_{ow} suggest that adsorption is not likely.

2.2.7. Bioaccumulation. Pertinent data regarding the bioaccumulation of chloroacetaldehyde in aquatic organisms were not located; however, estimated log K_{ow} and water solubility values suggest bioaccumulation would not be important.

2.2. AIR

Pertinent data regarding the environmental fate and transport of chloroacetaldehyde could not be located in the available literature as cited in the Appendix. Using the method of Atkinson (1985), the hydroxyl reaction rate constant was estimated to be 0.237×10^{-12} cm³/mol-sec. Assuming an ambient HO• concentration of 1×10^{6} molecules/cm³ (Cupitt, 1980), the HO• reaction half-life in the atmosphere was determined to be ~8 hours.

2.3. SOIL

Pertinent data regarding the fate and transport of chloroacetaldehyde under environmental conditions in soil could not be located in the available literature as cited in the Appendix. Stucki and Leisinger (1983) determined that Pseudomonas CElr degraded 2-chloroethanol to glycollic acid through chloroacetaldehyde (intermediary compound). However, the significance of this information with regard to biodegradation of chloroacetaldehyde under environmental conditions is uncertain. The soil sorption coefficient was calculated to be 60 using the molecular topology and quantitative structure-activity relationship analysis of Sabljic (1984). This K_{oc} value indicates that chloroacetaldehyde is likely to be highly mobile and susceptible to leaching through soils.

2.4. SUMMARY

Osterman-Golkar (1984) indicated that hydrolysis of chloroacetaldehyde is not an environmentally significant reaction ($t_{1/2}$>16 years). Volatilization has been predicted to be significant from shallow river waters, but it can be expected to take place slowly from other surface waters. Water solubility and K_{ow} data suggest that adsorption to suspended solids and sediments and bioaccumulation in aquatic organisms are not likely. The

estimated hydroxyl reaction half-life of 8 hours indicates that this reaction is probably a significant mechanism for removing chloroacetaldehyde from the atmosphere. Structural analysis of chloroacetaldehyde indicates that this compound is likely to be leached through soils.

3. EXPOSURE

No monitoring data are available to indicate ambient air or water levels, drinking water or food contamination or dermal exposure. Potential sources of chloroacetaldehyde entering the environment are from production and processing sites and use as a fungicide. Ando and Sayoto (1984) suggested that VCM can migrate from water pipes made of polyvinyl chloride; therefore, the reaction of VCM and chlorine is a possible source of chloroacetaldehyde in drinking water. Another possible source of chloroacetaldehyde in the atmosphere is formation from reaction of 1,3-dichloropropene with ozone and OH radicals (Tuazon et al., 1984). 1,3-Dichloropropene is a highly volatile component of widely used insecticidal fumigants (Tuazon et al., 1984).

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of chloroacetaldehyde could not be located in the available literature as cited in the Appendix.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of chloroacetaldehyde could not be located in the available literature as cited in the Appendix.

4.3. METABOLISM

Chloroacetaldehyde is a metabolite of a variety of halogenated organics (U.S. EPA, 1980a), which have received considerable study (Guengerich et al., 1980; Gwinner et al., 1983). The only metabolism study in which chloroacetaldehyde itself was administered to experimental animals was done by Green and Hathway (1977). Four adult Alderly-Park male rats were administered a 50 mg/kg aqueous solution of chloroacetaldehyde by gavage. An unspecified number of control animals was also used. Collected urine was divided for analysis into acetic acid and HCl fractions. The former fraction was analyzed by GC-mass spectometry and mass fragmentography for N-acetyl-S-(2-hydroxyethyl) cysteine, and the HCl fraction was analyzed by GC-mass spectometry for thiodiglycollic and chloroacetic acids.

The results allowed Green and Hathway (1977) to propose a scheme (Figure 4-1) for the metabolism of chloroacetaldehyde (the scheme is a portion of a more detailed metabolic pathway for vinyl chloride metabolism). Mass fragmentography revealed the presence of N-acetyl-S(2-hydroxyethyl) cysteine and S-(carboxymethyl) cysteine, but not chloroacetic acid, in the urine of treated rats. The urinary yield of thiodiglycollic acid, a derivative of S-(carboxymethyl) cysteine, was 9.2% of the administered dose of chloroacetaldehyde. Oral administration of S-(2-hydroxyethyl) cysteine to a

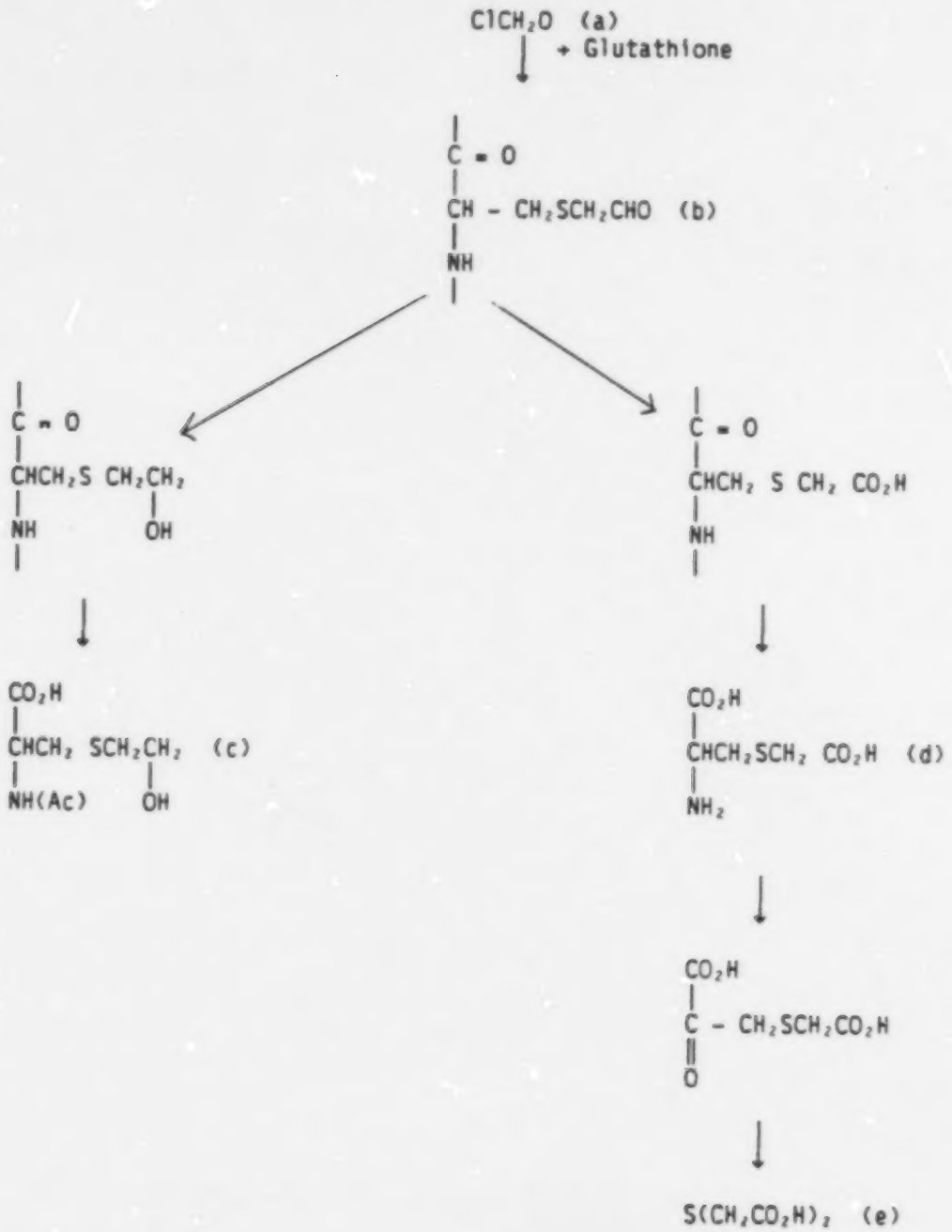


FIGURE 4-1

Proposed Scheme for the Metabolism of Chloroacetaldehyde

Source: Green and Hathway, 1977

separate group of rats led to a thiodiglycollic yield of only 0.5%. Green and Hathway (1977) therefore deduced that S-(carboxymethyl) cysteine was metabolized by a route independent of N-acetyl-S-(2-hydroxyethyl) cysteine, after chloroacetaldehyde administration.

According to Figure 4-1, chloroacetaldehyde (a) is conjugated to glutathione, to yield S-formylmethylglutathione (b). Further degradation and glutathionase activation results in the appearance of N-acetyl-S-(2-hydroxyethyl) cysteine (c). Alternatively, S-formyl-methylglutathione can be dehydrogenated and acted upon by liver and kidney glutathionases to yield S-(carboxymethyl) cysteine (d). Transamination followed by oxidative decarboxylation then leads to the major urinary metabolite, thiodiglycollic acid (e).

4.4. EXCRETION

As stated in Section 4.3., the three urinary metabolites observed after oral chloroacetaldehyde administration in rats were thiodiglycollic acid, S-(carboxymethyl) cysteine and N-acetyl-S-(2-hydroxyethyl) cysteine (Green and Hathway, 1977). No other information regarding other routes of elimination was located in the available literature.

4.5. SUMMARY

Pertinent data regarding the absorption, distribution or excretion of chloroacetaldehyde could not be located in the available literature as cited in the Appendix. Chloroacetaldehyde is a major metabolite of a number of chlorinated compounds (U.S. EPA, 1980a). After oral administration to rats, chloroacetaldehyde is first conjugated with glutathione and subsequently metabolized along two pathways (Green and Hathway, 1977). Urinary metabolites include N-acetyl(2-hydroxyethyl) cysteine, S-(carboxymethyl) cysteine and thiodiglycollic acid.

5. EFFECTS

5.1. CARCINOGENICITY

Van Duuren et al. (1979) conducted several carcinogenicity bioassays in chloroacetaldehyde-exposed male and female Ha:ICR Swiss mice. In the first study, 30 female mice/group were treated topically, 3 times/week on the shaved dorsal surface, with 1.0 mg/mouse chloroacetaldehyde in 0.1 mL acetone. The duration of treatment was 83 weeks. Untreated (100 mice) and acetone-treated control groups were also used. In a second study, 0.25 mg/mouse/week of chloroacetaldehyde in water was administered subcutaneously to 30 female mice for 90 weeks. Another group of 30 mice received 0.30 mg/mouse β-propiolactone, as a positive control, on the same schedule. Negative controls (100 mice) received nothing, water or trioctanoin (30 mice each). A third study involved weekly gastric intubation of 0.25 mg/mouse chloroacetaldehyde in water to 30 male and 30 female mice for up to 636 days (time of death of the last mouse). Mice treated with β-propiolactone or left untreated (100 females and 50 males) were used as controls.

All mice were examined daily and weighed monthly. They were necropsied upon termination of the experiment and all abnormal-looking tissues were analyzed histopathologically. In the study involving repeated skin applications, van Duuren et al. (1979) observed skin, liver, stomach and kidney tissue for pathology. In the intragastric studies, the stomach, liver, and kidneys were routinely analyzed. The major neoplasms of interest in subcutaneously-treated mice were local sarcomas (primarily fibrosarcomas).

Chloroacetaldehyde did not affect longevity by any route of administration. In the repeated skin application study, no treated mice had papillomas and the incidence of remote tumors was not significantly different from negative control mice. There were also no differences between treated

mice and negative controls in local sarcoma incidence after subcutaneous administration. In the subcutaneous study, the positive control mice had a statistically significant ($p<0.0005$) increase in tumor rate and decreased longevity, relative to negative controls.

As shown in Table 5-1, 3/30 intragastrically-treated females and 1/30 intragastrically-treated males had forestomach tumors; incidences were not different from negative controls. None of the tumors in the chloroacetaldehyde-treated mice were squamous carcinomas, and the rate of mortality was not adversely affected by treatment. β-propiolactone treatment significantly ($p<0.0005$) increased the incidences of both total forestomach tumors and squamous carcinomas, and decreased longevity.

Van Duuren et al. (1979) also studied the effects of chloroacetaldehyde in an initiation-promotion skin bioassay in Swiss mice. Chloroacetaldehyde, at a dose of 1.0 mℓ/mouse in 0.1 mℓ acetone, was applied to the shaved backs of 30 female mice. Fourteen days later, 2.5 μg of the tumor promotor PMA in 0.1 mℓ acetone was applied; subsequent PMA applications were done 3 times/week, for a total duration of ~60 weeks. Positive controls were administered 0.020 mg 7,12-dimethylbenz[a]anthracene (DMBA) as initiator, whereas negative controls received 0.0025 (120 mice) or 0.0050 (90 mice) mg/mouse of repeated PMA exposures. Papillomas were found in 3/30 chloroacetaldehyde-treated mice, which was not significantly different from the PMA controls (9/120 and 6/90 for the respective doses). A total of 317 papillomas were found in 29/30 DMBA-treated mice, which was a significantly higher ($p<0.0005$) tumor incidence than PMA controls.

Initiation-promotion studies were also begun on 8- to 10-week-old male XVIInc/Z mice (Zajdela et al., 1980). Groups of 20-28 mice each received single applications of chloroacetaldehyde in 80 μℓ acetone on their shaved

TABLE 5-1

Weekly Intragastric Administration of an Aqueous Solution of Chloroacetaldehyde to Ha:ICR Swiss Mice: Incidence of Forestomach Tumors[a]

Sex	Dose[b] (mg/mouse)	Duration of Treatment[c,d] (days)	Tumor Type	Tumor Incidence
M	0	636	all	8/60
F	0	649	all	5/100
M	0.25	636	all	1/30
F	0.25	630	all	3/30
M	0	636	squamous cell carcinoma	1/60
F	0	649	squamous cell carcinoma	0/100
M	0.25	636	squamous cell carcinoma	0/30
F	0.25	630	squamous cell carcinoma	0/30

QUALITY OF EVIDENCE

Strengths of Study: Lifetime exposure by relevant route. Large numbers of control animals. Positive controls used.

Weakness of Study: Only one, nontoxic dose given. Weekly administration. Limited number of endpoints explored.

Overall Adequacy: Inadequate

[a]Source: van Duuren et al., 1979

[b]Compound administered once a week

[c]Mice treated until moribund or found dead

[d]Duration of study equal to duration of treatment

backs. The doses were 2.5, 1.0, 0.1 or 0.05 mg/mouse. After initiation, promotion was effected by the use of 12-O-n-tetradecanoylphorbol-13-acetate (TPA), 3 times/week for 42 weeks. The animals were observed for ~84 weeks. The authors examined the mice for skin papillomas and carcinomas; the latter were characterized by invasion of the dermis. Twenty-eight mice received the same TPA application protocol but were not initiated with chloroacetaldehyde. Positive controls consisted of 45 mice receiving 50 µg DMBA in acetone, followed by thrice weekly promotion in croton oil for 12 weeks. These DMBA controls were observed for only 46-54 weeks.

Chloroacetaldehyde treatment did not affect longevity, relative to negative control (TPA only) rates. Only 7/45 positive control mice survived for an average observation period of 50 weeks, whereas 22/28 TPA controls lived for 84 weeks. Chloroacetaldehyde-treated mice had sporadic instances of short-lived (<4 weeks) papillomas, which were neither dose-related nor statistically different from negative controls. Only two mice (one each from the 1 and 0.1 mg groups) had papillomas that persisted 4 weeks after initial appearance, and none had skin carcinomas. In contrast, all mice treated with DMBA-croton oil showed some evidence of papillomatous lesions, and 37/45 had persistent papillomas or skin carcinomas or both.

Zajdela et al. (1980) concluded that chloroacetaldehyde may be too weakly electrophilic to initiate carcinogenic activity. However, they also noted that, because of its severe acute toxicity, chloroacetaldehyde may not have been tested effectively for demonstration of carcinogenic effect.

There were no other oral or inhalation carcinogenicity studies of chloroacetaldehyde. Lawrence et al. (1972), however, found evidence of premalignant changes in the respiratory epithelium of male Sprague-Dawley

rats treated intraperitoneally with 0.0016 or 0.0032 mℓ/kg of chloroacetaldehyde, 3 times/week for 12 weeks. Similarly, data on human occupational or epidemiological exposure could not be located in the available literature as cited in the Appendix.

5.2. MUTAGENICITY

Chloroacetaldehyde has been tested in a variety of mutagenic systems, as illustrated in Table 5-2. Both in the presence and absence of microsomal S9 mix, chloroacetaldehyde increased the number of revertants in Salmonella typhimurium strains (TA100, TA1530, TA1535) sensitive to base pair mutations (McCann et al., 1975; Bignami et al., 1980; Rannug et al., 1976; Malaveille et al., 1975). Similarly, in Bacillus subtilis, chloroacetaldehyde was effective in inducing revertants in a base pair sensitive (ilv B2), but not in a frameshift sensitive (leu A169) strain (Phillips et al., 1980). However, the doses used in these studies were often cytotoxic (Malaveille et al., 1975).

In other prokaryotic systems, chloroacetaldehyde was mutagenic to both normal and excision repair-deficient host cell reactivation strains of B. subtilis (Garro and Phillips, 1980). It was found to inhibit the growth of Escherichia coli pol A^+ and pol A^-, although inhibition was slightly greater for the pol A^- strain (Rosenkranz, 1977). Hussain (1984) demonstrated a dose-dependent increase in mutations to streptomycin nondependence in E. coli Sd-4 cultures. Cytotoxic doses of chloroacetaldehyde successfully reverted each of three E. coli strains to tryptophan prototrophy (Perrard, 1985). Finally, Bignami et al. (1980) showed that chloroacetaldehyde, could induce both forward and back mutations in a strain of Streptomyces coelicolor in a spot test, but not by plate incorporation.

TABLE 5-2

Mutagenicity Testing of Chloracetaldehyde

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA98, TA100 TA1535, TA1537 TA1538	NR	plate incorporation	~2-28 µg	-S-9	+	Highly mutagenic to TA100, weakly mutagenic to TA1535	McCann et al., 1975
Reverse mutation	S. typhimurium TA98, TA100 TA1535, TA1537 TA1538	45% aqueous solution	plate incorporation	3-60x10⁻⁴ µL/plate	±S-9	+/+	Positive in TA100. Addition of S-9 decreased response.	Bignami et al., 1980
Reverse mutation	S. typhimurium TA100,TA1535	45% aqueous solution	spot test	3-30 mg/plate	±S-9	+/+	Positive in TA100. Addition of S-9 decreased response.	Bignami et al., 1980
Reverse mutation	S. typhimurium TA1535	aqueous solution	plate incorporation	0.1-1.5 mM	-S-9	+	Dose-dependent increases in revertants at doses that were originally cytotoxic.	Rannug et al., 1976
Reverse mutation	S. typhimurium TA1530	50% aqueous solution	plate incorporation	0.4-40 µmoles/mL	±S-9	+/+	Highly cytotoxic at the highest concentration	Malaveille et al., 1975
Reverse mutation	Bacillus subtilis ilv B2, lev A169 markers	50% aqueous solution	plate incorporation (DNA transformation mixture)	0.25-5 mM	NR	+	Dose-dependent increase in mutation activity with base pair, but not with frameshift, mutation strain	Phillips et al., 1980
Forward mutation	B. subtilis φ105 strains G68 Gb7075	50% aqueous solution	plate incorporation	1-4 mM	NR	+	Mutagenic to both normal and repair-deficient host cell reactivation strains	Garro and Phillips, 1980
DNA repair	Escherichia coli pol A⁺ pol A⁻	NR	NR	10 µL	NR	+	Preferential inhibition of pol A⁻ growth	Rosenkranz, 1977
Forward mutation	E. coli Sd-4	dissolved in 0.2 M EtOH	NR	~0.1-4 mM·h	NR	+	Dose-dependent mutation to streptomycin nondependence	Hussain, 1984

TABLE 5-2 (cont.)

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	E. coli K12 A11 K12 A23 K12 A46	aqueous solution	liquid suspension	0.5-200 mM	none	+	Reversion frequency greatest near 100% cytotoxicity	Perrard, 1985
Reverse mutation	Streptomyces coelicolor A3(2) strain his A1	45% aqueous solution	plate incorporation and spot test	0.25-1.0 µl	none	+	Strongly mutagenic only in spot test	Bignami et al., 1980
Forward mutation	S. coelicolor A3(2) strain his A1	45% aqueous solution	plate incorporation and spot test	0.25-10 µl	none	+	Mutagenic only in spot test	Bignami et al., 1980
Forward mutation	Schizosaccharomyces pombe P1	50% aqueous solution	NR	0.78-6.25 mM	+S-9	+/+	Weak increase in mutation frequency	Loprieno et al., 1977
Gene conversion	Saccharomyces cerevisiae D4	50% aqueous solution	NR	3.1-12.5 mM	+S-9	±	Weak increase in mutation frequency at cytolethal concentrations	Loprieno et al., 1977
Polycistromic mutation	Aspergillus nidulans 35	45% aqueous solution	plate incorporation	20-40 µl	none	+	Mutagenicity not replicated in spot test	Bignami et al., 1980
Single point mutation	A. nidulans 35	45% aqueous solution	spot test	5-20 µl	none	+	Stronger induction of 8-azaquanine resistance in liquid test	Bignami et al., 1980
Forward mutation	CHO V79 cells	50% aqueous solution	liquid cultures	1.6-12.8 µM	NR	+	Much less mutagenic for ouabain resistance than 8-azaquanine resistance	Huberman et al., 1975

NR = Not reported

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In the yeast, Schizosaccharomyces pombe, either in the presence or absence of a mouse microsomal liver fraction, chloroacetaldehyde was weakly effective in inducing forward mutations for the biosynthesis of adenine (Loprieno et al., 1977). In the same study, frequency of gene conversions at the ade2 and try5 loci of Saccharomyces cerevisiae was marginally increased by increasing doses of this compound, only in the presence of S9 mix. Bignami et al. (1980) studied the effects of chloroacetaldehyde in inducing both single point (methionine suppression) or polycistionic (8-azaquanine resistance) genotoxicity, in Asperigillus nidulans haploid strain 35. Chloroacetaldehyde was effectively mutagenic in a liquid assay (for 8-azaquanine resistance) and a plate incorporation technique (for methionine suppression).

In CHO V79 cells in liquid suspension, chloroacetaldehyde was somewhat genotoxic for 8-azaquanine resistance but only slightly so for ouabain resistance (Huberman et al., 1975).

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of chloroacetaldehyde could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the other reproductive effects of chloroacetaldehyde could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The only information in the available literature regarding chronic oral administration of chloroacetaldehyde was provided by van Duuren et al. (1979). These authors found that the mortality rate of Ha:ICR Swiss mice was not affected by weekly gavage of 0.25 mg/mouse chloroacetaldehyde in water, compared with untreated controls. No other details were provided.

A subchronic study involving chloroacetaldehyde exposure (Dow, 1962) was unavailable for review but was briefly summarized by ACGIH (1980). Rats, guinea pigs, rabbits and mice were exposed by inhalation to chloroacetaldehyde at 1.6 ppm (5.1 mg/m³), 7 hours/day, 5 days/week for 6 months. No effects on growth, mortality, hematology or organ weights were observed. Gross and microscopic examination were unremarkable.

Lawrence et al. (1972) intraperitoneally administered a 0.5% aqueous solution of chloroacetaldehyde to male Sprague-Dawley rats 3 times/week for 12 weeks. The doses used were 0 0.00032, 0.0008, 0.0016 and 0.0032 mℓ/kg, calculated as pure chloroacetaldehyde. All groups consisted of 12 rats, except for the high dose, which had eight. Lawrence et al. (1972) observed the rats for mortality, and food consumption data were recorded during the 1st, 7th and 12th weeks. Hematological and BSP liver tests were conducted after the 12th week of dosing, and all survivors were sacrificed and necropsied. Organ-to-body weight ratios and histopathological examinations were done on eight selected tissue sites.

At the high dose, 5/8 rats died during the course of the study. At $\geq$0.0016 mℓ/kg, there was a significant ($p<0.01$) decrease in food consumption during the 1st week, which stabilized by the 7th week. There were no changes from control levels in either hematological or BSP values in rats given 0.00032 or 0.0008 mℓ/kg. Rats at the higher doses ($\geq$0.0016 mℓ/kg) showed significant increases in segmented neutrophils, and decreases in both erythrocytes and lymphocytes. Furthermore, the rats dosed with 0.00032 mℓ/kg showed a decline in hemoglobin concentration. Rats pretreated with 0.0016 mℓ/kg chloroacetaldehyde showed an elevated BSP elimination rate when tested 30-45 minutes after injection. No dose-related effects on organ-to-body weight ratios were found. Histological examination, however,

revealed that rats in the two highest dose groups had focal, chronic bronchopneumonia and evidences of premalignant changes in the respiratory epithelium. Pulmonary effects at the two lower doses and in the controls were far less severe and did not include epithelial atypia.

5.6. OTHER RELEVANT INFORMATION

Lawrence et al. (1972) conducted a series of toxicity studies using male ICR mice, S-D and Black Bethesda rats, Hartley guinea pigs and NZW rabbits, exposed to chloroacetaldehyde by any one of several routes. Although chloroacetaldehyde was given as an aqueous solution, doses were always expressed in terms of the pure compound. The LD_{50} after intragastric administration in rats and mice ranged from 0.06918-0.08665 mℓ/kg (82.3-103.1 mg/kg); intraperitoneal values in four species ranged from 0.00212-0.00827 mℓ/kg (2.5-9.8 mg/kg). Ten mice/exposure time were exposed for 1.44-4.40 minutes to 30% chloroacetaldehyde bubbled into an inhalation chamber. The LT_{50} was 2.57 minutes. In a separate study, 10 mice/group were pretreated with chloroacetaldehyde, either by intraperitoneal injection or by inhalation, on 3 consecutive days. At 24 hours after the last treatment, each mouse was injected with pentobarbital, and sleeping time was recorded as duration of loss of the righting reflex. Significant increases in sleeping time occurred at an inhalation concentration of 0.042 mg/m³ for 31 seconds, or an injection dose of 0.00061 mℓ/kg. Additional experiments suggested that these results were not an artifact of hepatic necrosis. Lawrence et al. (1972) further showed that a 0.002% chloroacetaldehyde concentration was not sensitizing in a guinea pig sensitization test. Whitehouse and Beck (1975), however, demonstrated that ingesting 1.0-2.5 µmol chloroacetaldehyde injected into the rat foot resulted in edema.

Border and Webster (1977) intravenously administered 0.5 mℓ of 0.2% chloroacetaldehyde, followed by [methyl-^{3}H]-thymidine, to partially hepatomectomized Wistar rats. The compound did not cause delayed incorporation of radioactivity into DNA.

In vitro, chloroacetaldehyde was found to effect cytotoxicity in murine L-cell and hemolysis in rabbit erythrocyte preparations (Lawrence et al., 1972).

5.7. SUMMARY

Chloroacetaldehyde has been found not to increase tumorigenesis when given repeatedly to mice by topical, subchronic or intragastric routes of administration (van Duuren et al., 1979). Weekly intragastric administration, using one dose level (0.25 mg/mouse), did not affect forestomach tumor incidence, relative to negative control rats. Administration of the positive control, β-propiolactone, on the same schedule significantly ($p<0.0005$) enhanced forestomach tumor incidence. By all routes of administration, chloroacetaldehyde did not affect longevity. Mortality rates were adversely affected by repeated β-propiolactone administration. A single initiation dose of chloroacetaldehyde, followed by thrice weekly promotion, did not increase the incidence of skin papillomas, relative to control rates (van Duuren et al., 1979; Zajdela et al., 1980). In none of these studies were attempts to define a dose-effect relationship made. There were no data regarding human occupational or epidemiological exposure to chloroacetaldehyde.

Chloroacetaldehyde has been found to be mutagenic in *Salmonella typhimurium* (McCann et al., 1975), *Bacillus subtilis* (Phillips et al., 1980), *Escherichia coli* (Rosenkranz, 1977), and *Streptomyces coelicolor* (Bignami et al., 1980) prokaryotes, and also in *Schizosaccharomyces pombe* (Loprieno et

al., 1977), Saccharomyces cerevisiae (Loprieno et al., 1977), and Aspergillus nidulans (Bignami et al., 1980) eukaryotes. It was moderately genotoxic to cultured CHO ovary cells (Huberman et al., 1975). In many of these studies, the genotoxic effect was weak and specific for base-pair mutations. Additionally, the severe acute toxicity of chloroacetaldehyde may mask significant mutagenic expression.

There were no studies in the available literature regarding the reproductive effects of chloroacetaldehyde exposure.

Van Duuren et al. (1979) administered chloroacetaldehyde at a dose level of 0.25 mg/mouse once a week for life. There were no effects of this dose on longevity. Inhalation exposure to 1.6 ppm (5.1 mg/m^3) chloroacetaldehyde, 7 hours/day, 5 days/week for 6 months had no observable adverse effects on rats, guinea pigs, rabbits or mice (Dow, 1962).

Lawrence et al. (1972) administered chloroacetaldehyde by intraperitoneal injection to Sprague-Dawley rats, 3 times/week for 12 weeks. Upon necropsy, predominant among rats given the high doses (0.0016 and 0.0032 mℓ/kg) were hematological changes and bronchopneumonia. In rats treated with 0.00032 or 0.0008 mℓ/kg, there were no remarkable treatment related effects.

Chloroacetaldehyde has been found to be acutely lethal at low levels; the oral LD_{50} in rats and mice ranged from 82.3-103.1 mg/kg. Increased pentobarbital-induced sleep time in mice exposed by inhalation to 0.043 mg/m^3 for 31 seconds was also noted (Lawrence et al., 1972).

6. AQUATIC TOXICITY

6.1. ACUTE

Little information is available about the toxicity of chloroacetaldehyde to aquatic organisms. Bengtsson and Tarkpea (1983) reported that the 96-hour LC_{50} for the harpaeticoid copepod, Nitocra spinipes, was 1.5 mg/ℓ. Applegate et al. (1957) reported that no signs of distress were observed in sea lampreys, Petromyzon marinus, exposed to 5 mg/ℓ for 24 hours.

6.2. OTHER RELEVANT INFORMATION

Pertinent data regarding chronic toxicity, plant effects and residues of chloroacetaldehyde in aquatic biota could not be located in the available literature as cited in the Appendix.

6.3. SUMMARY

Little information is available about the toxicity of chloroacetaldehyde to aquatic organisms. The 96-hour LC_{50} for the copepod, Nitocra spinipes, was 1.5 mg/ℓ (Bengtsson and Tarkpea, 1983), but sea lampreys were unaffected by exposure to 5 mg/ℓ for 24 hours (Applegate et al., 1957).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Because of chloroacetaldehyde's severely corrosive and irritating nature (see Section 5.6.), a ceiling limit of 1 ppm (~3 mg/m^3) has been recommended (ACGIH, 1980) for human occupational exposure. The ACGIH (1980) warned that this level may not prevent all complaints of irritation, and, because of its mutagenic activity, continuous exposure was discouraged. The ceiling limit was adopted by the ACGIH (1985). The permissible exposure limit for chloroacetaldehyde recommended by OSHA (1985) is also 1 ppm.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from chloroacetaldehyde toxicity could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Oral administration of 45% chloroacetaldehyde, once a week for up to 636 days, to 30 male and 30 female Ha:ICR Swiss mice, did not increase either forestomach total tumor or squamous carcinoma incidence, relative to negative controls (van Duuren et al., 1979). Longevity was also not affected by treatment. The single dose level used was 0.25 mg/mouse/week. Thirty mice of each sex receiving the positive control substance, β-propiolactone, on a weekly basis had statistically significant ($p<0.0005$) increases in both total forestomach tumors and squamous carcinomas. This study suffered from an inadequate number of mice in each group and the absence of complete dose-effect data. It is therefore inadequate for assessment of the carcinogenic potential of chloroacetaldehyde.

Other studies (van Duuren et al., 1979; Zajdela et al., 1980) have shown that repeated exposure to chloroacetaldehyde is not carcinogenic by topical or subcutaneous routes. Under the conditions of these experiments, it was also noncarcinogenic when used as an initiator in tumor promotion studies.

Chloroacetaldehyde has been found to be genotoxic to S. typhimurium and B. subtilis strains that are sensitive to base pair mutations (McCann et al., 1975; Phillips et al., 1980; Bignami et al., 1980; Rannug et al., 1976). In E. coli, it selectively inhibited the growth of a polymerase-deficient strain (Rosenkranz, 1977) and reverted three strains to tryptophan prototrophy (Perrard, 1985). In yeast, chloroacetaldehyde was marginally effective in inducing forward mutations and gene conversions (Loprieno et al., 1977). Both single point and polycistronic mutations were observed after chloroacetaldehyde treatment of A. nidulans. Huberman et al. (1975) found evidence for increased mutagenicity to 8-azaquanine resistance in

cultured CHO ovary cells treated with chloroacetaldehyde. In many of these studies the extent of genotoxicity was minor and occurred only at highly cytotoxic doses.

There were no data in the available literature regarding the teratogenic or reproductive toxicity of chloroacetaldehyde.

Van Duuren et al. (1979), while orally dosing 30 male and 30 female Ha:ICR Swiss mice with 0.25 mg/mouse/week chloroacetaldehyde for life, observed that chloroacetaldehyde did not alter longevity compared with negative controls. The dosing schedule was suggestive of repeated acute, rather than chronic, exposure, and is of little value in assessment of chronic toxicity.

At an inhalation concentration of 1.6 ppm (5.2 mg/m^3), rats, rabbits, mice, and guinea pigs were exposed to chloroacetaldehyde 7 hours/day, 5 days/week, for 6 months (Dow, 1962). There were no adverse effects on growth, mortality or organ weights. Hematological and histological analyses were unremarkable.

The oral carcinogenicity bioassay of van Duuren et al. (1979) was inadequately designed for assessment of the tumorigenic potential of chloroacetaldehyde. It would be appropriate to derive an ADI, rather than a q_1^*, until adequate carcinogenicity data are available.

Because data regarding the effects of chronic or subchronic oral exposure to chloroacetaldehyde were not available, an ADI can be derived from the Dow (1962) inhalation study. Results suggest a NOEL in each of four species subchronically exposed to 1.6 ppm (5.1 mg/m^3), 7 hours/day, 5 days/week for 6 months. Using the guidelines recommended by the U.S. EPA (1980b), this concentration can be converted into an equivalent daily dose for each species. Given standard body weights and inhalation rates for mice

(0.03 kg; 0.039 m^3/day) and rats (0.35 kg; 0.023 m^3/day) (U.S. EPA, 1980b), and rabbits (3.8 kg; 2.0 m^3/day) and guinea pigs (0.84 kg; 0.40 m^3/day) (Durkin, 1985), assuming each animal absorbs 50% of what it inhales and correcting for continuous exposure, the NOEL corresponds to 0.691, 0.338, 0.280 and 0.253 mg/kg/day for mice, rats, rabbits and guinea pigs, respectively. Because the dose of 0.69 mg/kg/day for mice is the highest NOEL, it is appropriate to use it in ADI derivation. Application of an uncertainty factor of 1000 (10 for the duration of exposure, 10 for intraspecies extrapolation and 10 for sensitive subgroups) results in an ADI of 0.007 mg/kg/day or 0.49 mg/day for a 70 kg man.

The NOEL receives some support from the work of Lawrence et al. (1972). At intraperitoneal doses of 0.0016 and 0.0032 mℓ/kg, 3 times/week, rats showed a variety of hematological and pulmonary changes (see Section 5.5.). Given the specific gravity of 1.19 for chloroacetaldehyde, these values correspond to 1.9 and 3.8 mg/kg (or 0.8 and 1.6 mg/kg/day, expanded over a 7-day week), respectively. At 0.0008 mℓ/kg, or 0.95 mg/kg (0.4 mg/kg/day), there were no hematological effects and no atypia of the respiratory epithelium.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

A review of results based upon chronic and subchronic toxicity testing of chloroacetaldehyde is provided in Section 5.5. The only information regarding lifetime exposure to chloroacetaldehyde was provided by van Duuren et al. (1979), where mice gavaged weekly with 0.25 mg/mouse of chloroacetaldehyde lived as long as untreated controls.

Dow (1962) found that mice, rats, rabbits and guinea pigs were unaffected by exposure to 1.6 ppm (5.1 mg/m^3) chloroacetaldehyde, 7 hours/day, 5 days/week for 6 months. The animals were examined for body and organ weight changes, hematological effects, mortality, and gross and histopathological lesions.

A 12-week intraperitoneal study in rats revealed effects of chloroacetaldehyde on hematology, liver function tests and pulmonary histopathology at $\geq$0.0016 mL/kg ($\geq$1.9 mg/kg) 3 days/week (Lawrence et al., 1972). Because of the route of exposure, however, these data are not germane to the derivation of an RQ.

As the chloroacetaldehyde levels used in the oral and inhalation studies were below the threshold of observable toxicity, the data are insufficient for derivation of an RQ (Table 9-1).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

As reviewed in Section 5.1. and presented in Table 5-1, the carcinogenicity of chloroacetaldehyde in experimental animals has not been adequately studied. The only lifetime oral study available was provided by van Duuren et al. (1979), who administered 0.25 mg chloroacetaldehyde/mouse by gavage to 30 male and 30 female mice on a weekly basis. Compared with negative controls, there were no increases in either total forestomach tumors or

TABLE 9-1

2-Chloroacetaldehyde

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ.

squamous carcinomas in treated mice. Positive control mice (60) showed a highly significant ($p<0.0005$) increase in both of these tumor incidences. Because of the small number of mice in the treated groups, the lack of a dose curve and the limited number of endpoints explored, this study was not adequate to assess the carcinogenicity of chloroacetaldehyde.

Chloroacetaldehyde was also negative as a whole carcinogen in a skin painting bioassay in mice, and a tumor initiator, using PMA as a promotor (van Duuren et al., 1979). No increased incidence of sarcomas was observed in mice injected subcutaneously weekly for 90 weeks.

Lawrence et al. (1972), however, found evidence of premalignant changes in the respiratory epithelium of male Sprague-Dawley rats treated intraperitoneally with 0.0016 or 0.0032 mL/kg, 3 times/week for 12 weeks.

Because of its limited data base, chloroacetaldehyde should be assigned an IARC Group 3 classification. Structurally related compounds, such as formaldehyde and acetaldehyde, are known to be carcinogenic. Unlike these related compounds there is no inhalation data available to show carcinogenic activity of chloroacetaldehyde. Chloroacetaldehyde is mutagenic and a presumed intermediate in metabolic pathway of EDC (ethylenedichloride). Because of lack of enough evidence for its carcinogenicity, the overall weight of evidence indicates that chloroacetaldehyde could be classified as a possible carcinogen (CAG Group C) or not classifed as a human carcinogen (CAG Group D) (U.S. EPA, 1984). Accordingly, Group D compounds cannot be ranked on the CERCLA hazard ranking scheme.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS onliine STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., CITY, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

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